Experimental and theoretical comparison of addition-fragmentation pathways of diseleno- and dithiocarbamate RAFT agents

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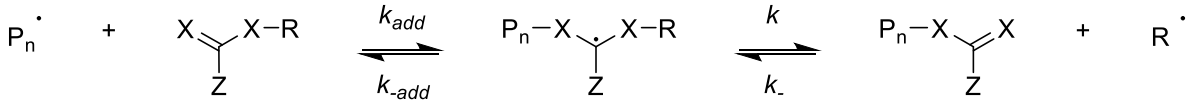
ABSTRACT. Theoretical studies suggest that identically substituted dithio- and diselenocarbamate RAFT agents will have similar reactivity, but that diselenocarbamate RAFT agents are more likely to undergo intermediate radical termination. These results are supported by an experimental study of polymerizations of vinyl acetate mediated by *Se*-cyanomethyl *N*,*N*-dimethyl diselenocarbamate (**1Se**) and its sulfur analog, *S*-cyanomethyl *N*,*N*-dimethyl

dithiocarbamate (**1S**). While the two polymerizations had similar interchain transfer constants (3.2 for **1S** and 3.9 for **1Se**), significant retardation was observed for **1Se**-mediated polymerizations. External chain transfer constants were also measured for **1S** (5.4) and **1Se** (45). The low apparent value of the chain transfer constant of **1S** is attributed to the selective formation of a single monomer adduct in the early stages of the reaction.

Introduction

Reversible-addition fragmentation chain transfer polymerization (RAFT) is now one of the most widely used reversible deactivation radical polymerization techniques, both academically[1] and industrially.[2] RAFT relies on the use of a reversible chain transfer agent, comprising a homolytic leaving group, R, a radical stabilizing group, Z, and an unsaturated central group, shown as X=C-X in Scheme 1. A wide variety of RAFT agents are available, and the effects of varying R and Z groups have been thoroughly studied, both experimentally[3-6] and theoretically.[7-10] The effect of changing the central group is much less well-understood.



Scheme 1 Chain transfer reactions in RAFT polymerization (X = CH_2, S, Se)

Chain transfer reactions between growing polymer chains and the RAFT agent are at the heart of the RAFT process. There are two major chain transfer reactions, shown in Scheme 1. The first, known as the pre-equilibrium, involves the transformation of the RAFT agent into a polymeric macroRAFT agent. The second is a degenerate chain transfer reaction between a propagating chain and a macroRAFT agent.

Chain transfer constants can be associated with each equilibrium, and are defined in equations 1 and 2 (k_p represents the propagation rate constant, other rate constants are defined in Scheme 2):[11]

$$C_S = \frac{k_{add}}{k_p}\frac{k_\beta}{k_{-add}+k_\beta} \quad (1)$$

$$C_{ex} = \frac{k_{add}}{2k_p} \quad (2)$$

A reverse chain transfer constant can also be defined for the pre-equilibrium, governing the reaction of leaving group derived radicals (R•) with the macroRAFT agent to regenerate RAFT agent and a propagating radical (equation 3, k_i represents the rate constant of addition of R• to monomer):

$$C_{-S} = \frac{k_{-\beta}}{k_i}\frac{k_{-add}}{k_{-add}+k_\beta} \quad (3)$$

In an ideal RAFT polymerization, C_S and C_{ex} are high, leading to rapid formation of the macroRAFT agent and interconversion between macroRAFT agents and propagating chains, while C_{-S} is negligible. An induction period during which little or no polymerization occurs is sometimes observed during the pre-equilibrium step, as the original RAFT agent is selectively converted to a single monomer adduct.[12-15]

As shown in Scheme 1, the RAFT equilibrium takes place *via* formation of an intermediate radical adduct. Ideally, this would be a short-lived species that does not undergo any reaction other than fragmentation. Observations of retardation in many RAFT polymerizations led to a debate over the true role of the intermediate radical adduct. Barner-Kowollik and Davis[16] suggested that slow fragmentation of the RAFT adduct could explain the retardation observed in styrene polymerizations mediated by dithiobenzoate RAFT agents. However, the very high intermediate radical adduct concentrations that would result from slow fragmentation were not observed in EPR experiments.[17] In order to reconcile these data, Monteiro proposed that the intermediate radical undergoes termination reactions with itself and with propagating radicals.[18] This approach can explain the observed retardation in a manner that is consistent with EPR results, but should result in the formation of 3- and 4-arm star polymers that are not observed in the experimental MWD. A number of other theories have been advanced to explain this absence. These include the 'Missing Step' model of Buback et al.,[19] in which it is postulated that 3-arm stars formed via intermediate radical termination may react with propagating radicals to reform the intermediate radical adduct and a dead polymer chain, and the short radical termination model of Konkolewicz and Perrier[20] in which it is postulated that long chain radicals are too sterically hindered to react with the intermediate radical adduct, and thus that intermediate radical termination involves only oligomeric and initiator-derived radicals that produce 3-arm stars that are indistinguishable from dead chains produced by radical combination. . Additionally, Coote and Barner-Kowollik showed that entropic effects lead to strong chain length dependencies polymer-polymer reactions, even when they are chemically controlled. They suggested these effects could easily explain differences in fragmentation rate coefficients between the early stages of polymerization and the macroRAFT EPR experiments.[21] The true mechanism causing retardation remains unresolved, and may vary

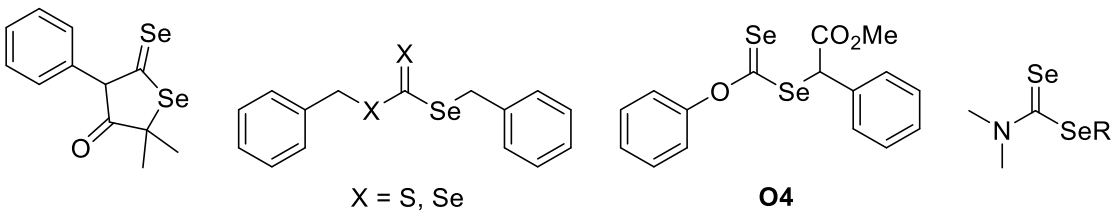
depending on the combination of monomer and RAFT agent used. More detailed discussion of this topic may be found in recent reviews[15,22,23]

The first reports of reversible chain transfer as a means of controlling polymerization used macromonomers of methacrylic acid or methyl, *t*-butyl or phenyl methacrylate as chain transfer agents.[24] In this case X = CH_2. Subsequent studies investigated a range of different methacrylate- and α-methyl styrene-based dimer, trimer and macromonomer RAFT agents, typically finding chain transfer constants of 0.1-0.5 in polymerizations of styrene (St), acrylates and methacrylates.[25] To achieve control of dispersity and molecular weight with such low chain transfer constants required the use of starved-feed conditions to favor chain transfer over polymerization, in emulsion polymerization to limit termination reactions. With appropriate choice of reaction conditions, complex and well-controlled structures can be obtained using these chain transfer agents.[26]

Sulfur-based chain transfer agents (X = S), introduced in 1998, exhibit much higher chain transfer constants, allowing controlled polymerization to be achieved in solution under batch conditions. Experimental[27] and theoretical[28] studies have also examined control agents based on dithiophosphinate esters (i.e., S=P-S-R) but with limited success. The vast majority of currently used RAFT agents incorporate a thiocarbonylthio (S=C-S) group.

Several recent papers have investigated the use of selenium as an alternative to sulfur (Scheme 2). Selenium-based RAFT agents allow the preparation of selenol-functional polymers which can be used to access the interesting biological and redox properties of the diselenide[29] group. Zhan et al.[30] reported the use of a cyclic diselenocarbamate in the polymerization of vinyl acetate (VAc) , while Zeng et al.[31] have studied the use of *S*,*Se*-dibenzyl selenodithiocarbonate, *S*,*Se*-dibenzyl diselenothiocarbonate and dibenzyl triselenocarbonate (also studied by Botha et al.[32] in the

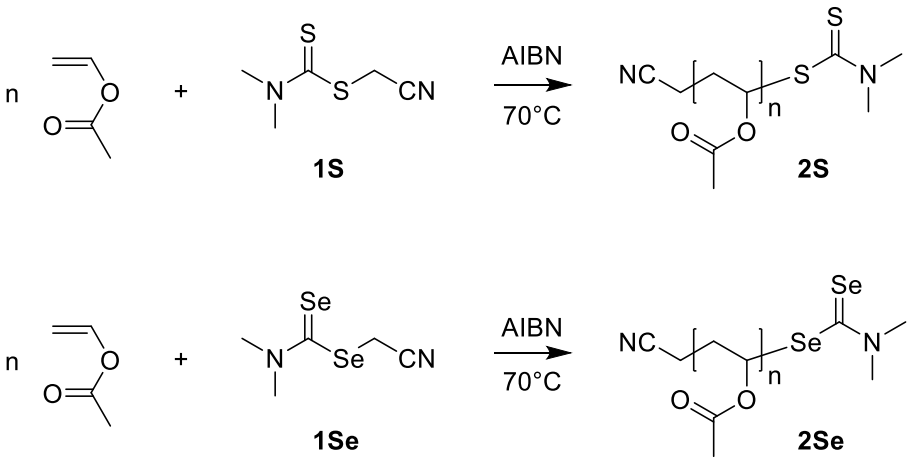
polymerization of St. Zeng et al. also studied a series of diselenocarbonates, analogous to xanthate RAFT agents, in particular the *O*-phenyl *Se*-1-methoxycarbonylbenzyl diselenocarbonate **O4** (Scheme 2), which could control the polymerization of a wide range of monomers, including styrene, acrylates and vinyl esters.[33] Our own group[34] reported the use of *Se*-benzyl, *Se*-1-phenylethyl and *Se*-cyanomethyl *N*,*N*-dimethyl diselenocarbamates to control the polymerization of St, butyl acrylate, VAc, vinyl pivalate and N-vinyl caprolactam. In each of these reports, similar levels of control over molecular weight and dispersity were achieved using either sulfur-based RAFT agents or their selenium analogs. However, use of selenium-based RAFT agents gave slower reactions: polymerization of St in the presence of the triselenocarbonate proceeded at approximately half the rate of the polymerization in the presence of the same quantity of trithiocarbonate. This was ascribed to higher levels of side reactions such as termination in the presence of selenium-based RAFT agents.[31]



Scheme 2. Selenium-based RAFT agents.[10-14]

In order to investigate the effect of selenium in more detail, we have carried out detailed kinetic studies of the polymerization of VAc in the presence of *Se*-cyanomethyl *N*,*N*-dimethyl diselenocarbamate (**1Se**) and its sulfur analog, *S*-cyanomethyl *N*,*N*-dimethyl dithiocarbamate (**1S**) as shown in Scheme 3. These experiments were aimed at determining the chain transfer constants of the RAFT agents and dormant polymer chains, as well as quantifying the effect of each RAFT agent on the rate of polymerization. To support these experiments a series of theoretical

calculations were also undertaken to compare the underlying similarities and differences in selenium- and sulfur-based RAFT agent reactivities.



Scheme 3. RAFT polymerization of vinyl acetate mediated by 1S or 1Se.

Theoretical Results and Discussion.

To explore the underlying fundamental differences in reactivity between the C=S and C=Se bonds, gas-phase quantum-chemical calculations to study the simplest possible analogs of their respective RAFT reactions; namely, methyl radical addition to methyl dithioformate and methyl diselenoformate (Table 1). The results suggest that Se-based RAFT agents should undergo radical addition reactions that are both faster (due to their lower free energy barrier) and more exothermic than those of S-based RAFT agents. This is understandable in terms of the weaker C=Se versus C=S π-bond strengths, resulting from poorer orbital overlap between the 2p(C) and 4p(Se) orbitals of C=Se, versus the 2p(C) and 3p(S) orbitals of C=S. These trends are a logical extension of those examined previously for C=O versus C=S radical addition.[35] If these trends are preserved in the reactions of substituted radicals and control agents, then the faster radical addition to Se-based

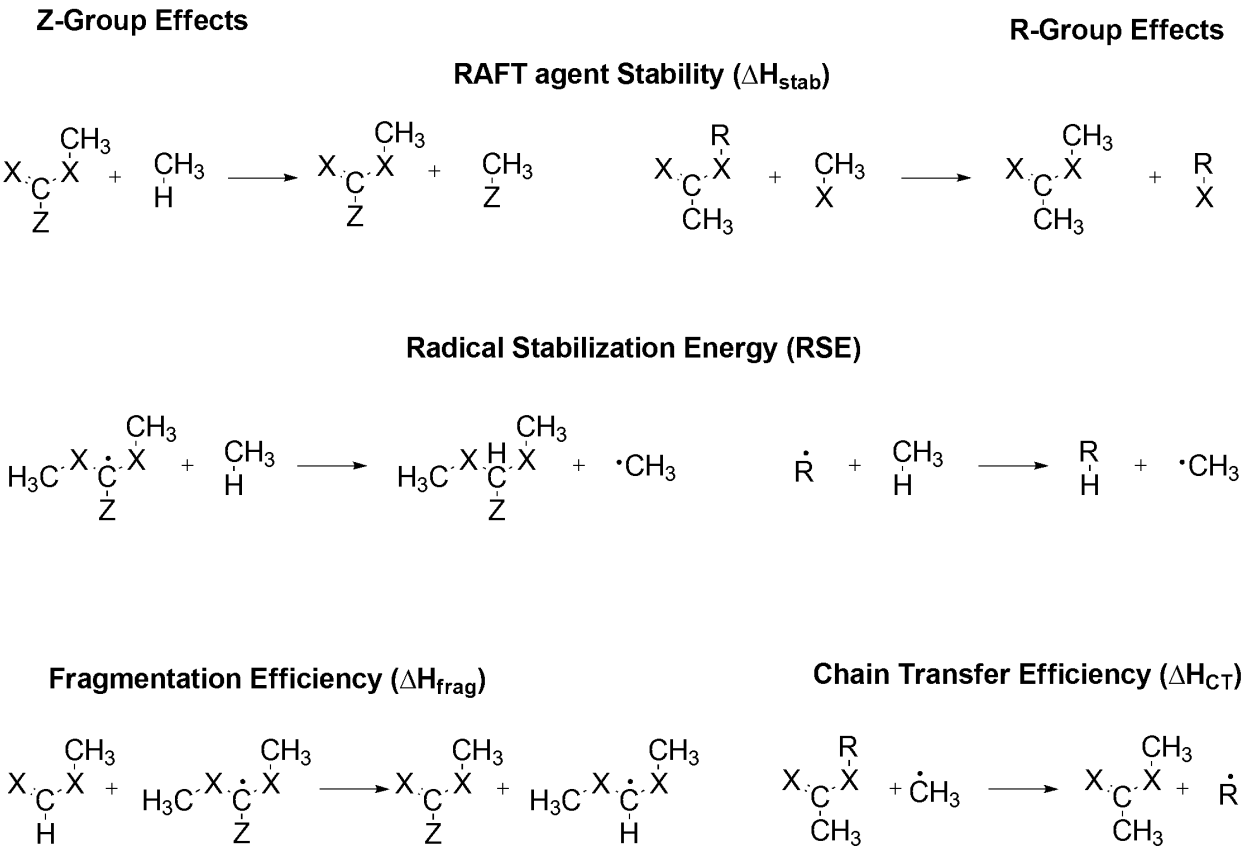
RAFT agents should deliver improved control, while the greater stability of the adduct radical would lead to more retardation relative to S-based RAFT agents.

Table 1. Enthalpies (H) and Gibbs free energies (G) of reaction (ΔH, ΔG) and activation ($\Delta H^{\neq}$, $\Delta G^{\neq}$) for methyl radical addition to methyl dithioformate and methyl diselenoformate (298.15K, kJ mol^{-1})[a]

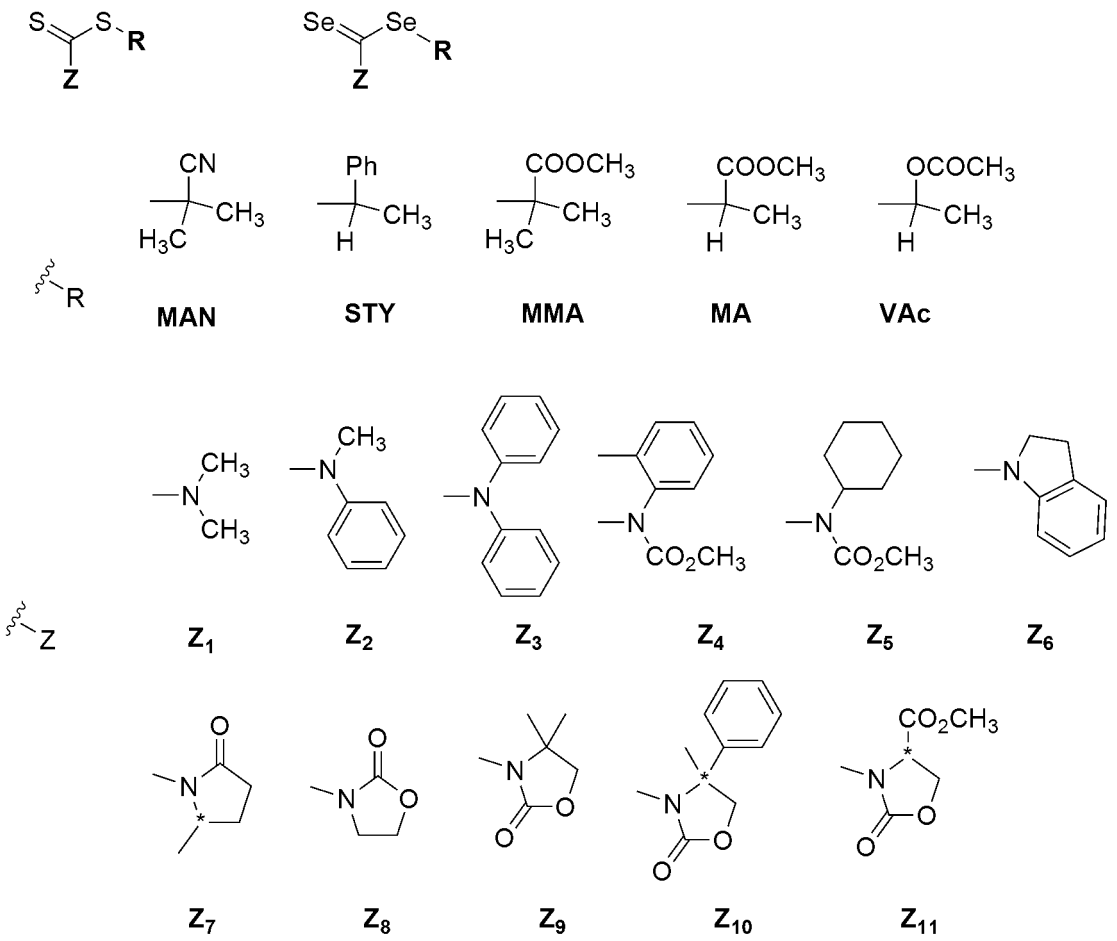
Substrate	ΔH	$\Delta H^{\neq}$	ΔG	$\Delta G^{\neq}$
S=C(H)SCH$_3$	-74.7	18.7	-39.8	42.4
Se=C(H)SeCH$_3$	-91.6	-7.0	-56.1	26.3

[a]Calculated at the G3(MP2)-RAD//M06-2X/6-31G(d) level of theory in the gas phase. For both reactions, the addition transition state is a first order saddle point with a positive barrier at M06-2X/6-31G(d) but in the case of the Se derivative, the improved G3(MP2)-RAD energies result in a negative enthalpic barrier, though the Gibbs free energy barrier remains positive due to the loss of entropy on forming the transition state.

To assess whether the change from S to Se affects structure-reactivity trends, we calculated a series of reactivity descriptors that were originally developed[36,37] as a simple semi-quantitative predictor of the kinetic behavior of a new RAFT agent relative to known compounds. It is important to note that these descriptors measure the effects of changing R or Z separately using simplified model compounds, and assume that any specific interactions between R and Z groups are negligible. For the Z-group effects, we calculated descriptors for the RAFT agent stability (ΔH_{stab}), the radical stabilization energy (RSE) of RAFT-adduct radical, and its fragmentation efficiency (ΔH_{frag}). For the R-group effects, we calculated an equivalent ΔH_{stab} descriptor, the RSE of R$^{\bullet}$ leaving radical, and its chain transfer efficiency (ΔH_{CT}). The definitions of these terms are provided in Scheme 4,[36] and the R and Z groups studied are shown in Scheme 5. Figure 1 compares corresponding values of each type of descriptor for dithiocarbamates and diselenocarbamates; full data is provided in the ESI.



Scheme 4. Descriptors for modelling the effects of the Z- and R- groups on RAFT Agent Stability (ΔH_{stab}) and Radical Stabilization Energy (RSE), the effect of Z-group on Fragmentation Efficiency (ΔH_{frag}) and the effect of R-group on Fragmentation Efficiency (ΔH_{CT}).[36] In this work we consider cases where X=S or Se.



Scheme 5. R- and Z-groups studied theoretically.

The R-group descriptors of corresponding dithiocarbamates and diselenocarbamates are essentially identical, while the Z-group descriptors are highly correlated, indicating that R and Z substituents have similar effects on the reactivity of dithio- and diseleno-carbamates.

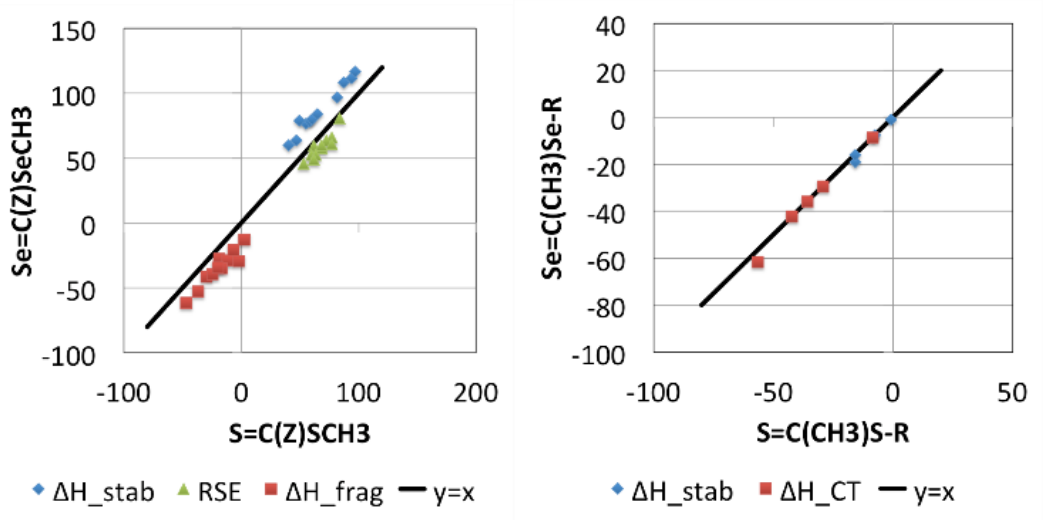
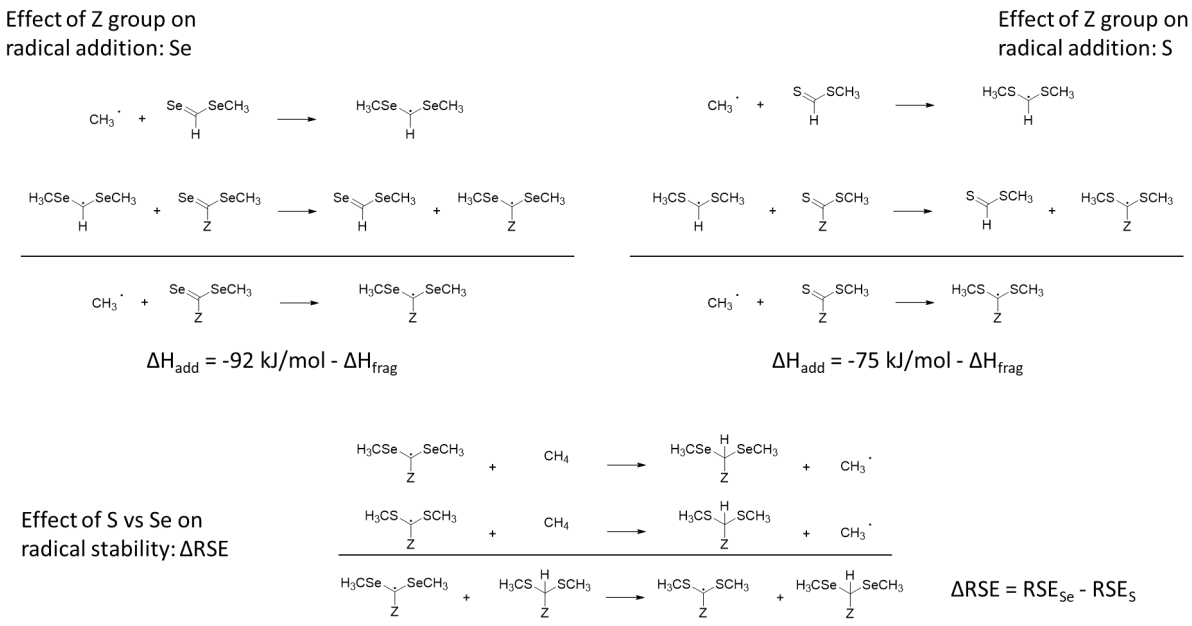


Figure 1. Comparison of corresponding reactivity descriptors for dithiocarbamates and diselenocarbamates. The plot on the left shows Z-group descriptors (RSE of RAFT-adduct radical, ΔH_{frag} and ΔH_{stab}) while that on the right shows R-group descriptors (RSE of RAFT-adduct radical, ΔH_{frag} and ΔH_{stab})

To probe the differences between the two classes of RAFT agent, new descriptors were obtained by combining the Z group descriptors with the enthalpies of methyl radical addition to the model sulfur and selenium-based RAFT agents of Table 1. These were ΔH_{add} for addition of a methyl radical to the RAFT agent, and ΔRSE for the difference in radical stabilization energy between dithio- and diseleno-RAFT adduct radicals (Scheme 6).



Scheme 6. Descriptors for comparison of dithio- and diselenocarbamate RAFT agents: enthalpy of addition of methyl radical (ΔH_{add}) and hydrogen transfer from dithioacetal to diselenocarbamate radical adduct (ΔRSE).

Figure 2 shows that, for most Z-groups investigated, including dimethylamino (Z_1), the enthalpies of methyl addition to dithio- or diseleno-carbamates are essentially identical. The higher ΔH_{frag} observed for diselenocarbamates are almost exactly compensated by the difference of 16.9 kJ.mol^{-1} in ΔH of methyl addition to methyl dithioformate vs methyl diselenoformate (Table 1).

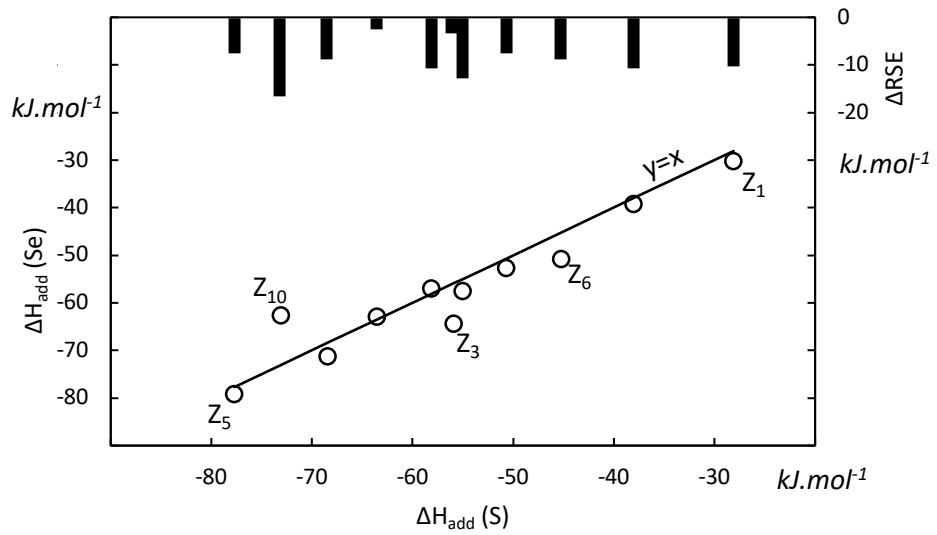


Figure 2. Comparison of enthalpy of methyl radical addition (ΔH_{add}) for dithio- and diselenocarbamates. The bars represent the enthalpy of hydrogen transfer from a dithioacetal to a diselenocarbamate radical adduct (ΔRSE).

On the other hand, ΔRSE ranges from -16 to -3 kJ.mol^{-1}, indicating that the dithiocarbamate radical adducts are more stable than diselenocarbamate radical adducts with respect to combination with other radicals to form dithio- or diseleno-ketal type products. These results suggest that identically substituted dithio- and diselenocarbamates should show similar reactivities in radical polymerizations, but that radical adducts derived from diselenocarbamates may be more prone to undergo intermediate radical termination through combination with other radicals.

Experimental Results and Discussion

Effect of RAFT agent on kinetics of polymerization. We subsequently carried out an experimental study of two analogous RAFT agents, *S*-cyanomethyl *N*,*N*-dimethyl dithiocarbonate (**1S**) and *Se*-cyanomethyl *N*,*N*-dimethyl diselenocarbamate (**1Se**), as chain transfer agents in the

RAFT polymerization of VAc. Both RAFT agents provided good control over molecular weight, with good agreement between experimental and theoretical number-average degrees of polymerization (Figure 3). Dispersities, though sometimes very large at the beginning of the polymerization, were around 1.5 at conversions of 40% and above. These characteristics are typical of moderately active RAFT agents in the polymerization of vinyl esters.[38] Full details of molecular weight and dispersity can be found in the Supporting Information.

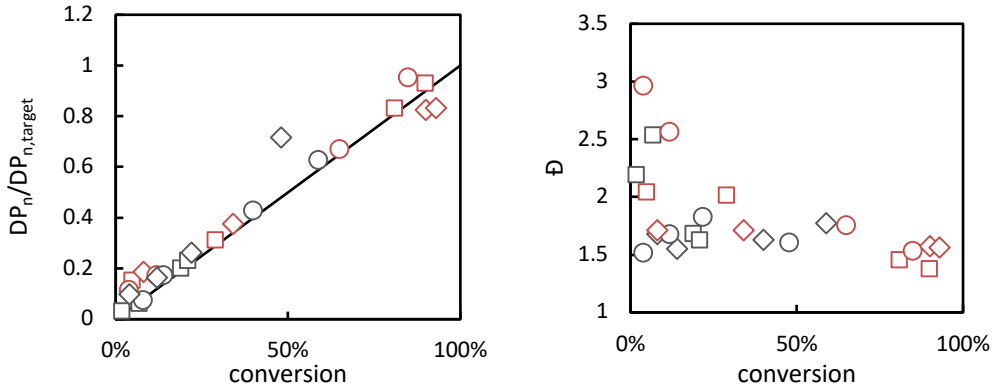


Figure 3. Evolution of normalized number-average degree of polymerization and dispersity with conversion for bulk vinyl acetate polymerizations mediated by **1S** (red) and **1Se** (grey) in the presence of 11 mM AIBN at 70 °C. Different symbols correspond to different initial VAc:**1** ratios (**1S:** square: 442:1; diamond: 233:1; circle: 114:1; **1Se:** square: 464:1; diamond: 231:1; circle: 114:1).

1S and **1Se** both slowed the rate of VAc polymerization, but in different ways. Addition of **1S** resulted in an induction period, t_0, of up to 2 h, followed by polymerization at a reduced rate compared to the control polymerization without added RAFT agent (Figure 4). Addition of **1Se** did not cause a significant induction period but led to severe retardation: the polymerization in the presence of 0.1 M **1Se** was approximately 100 times slower than the control polymerization. Further details of the fitting procedure can be found in the Supporting Information.

The retardation of the polymerization indicates that the concentration of propagating radicals is decreased in the presence of both **1S** and **1Se**. This is most likely a result of intermediate radical termination,[18,22] which appears much more pronounced in the case of **1Se**-mediated polymerizations, and may even be the dominant mode of termination in this reaction.

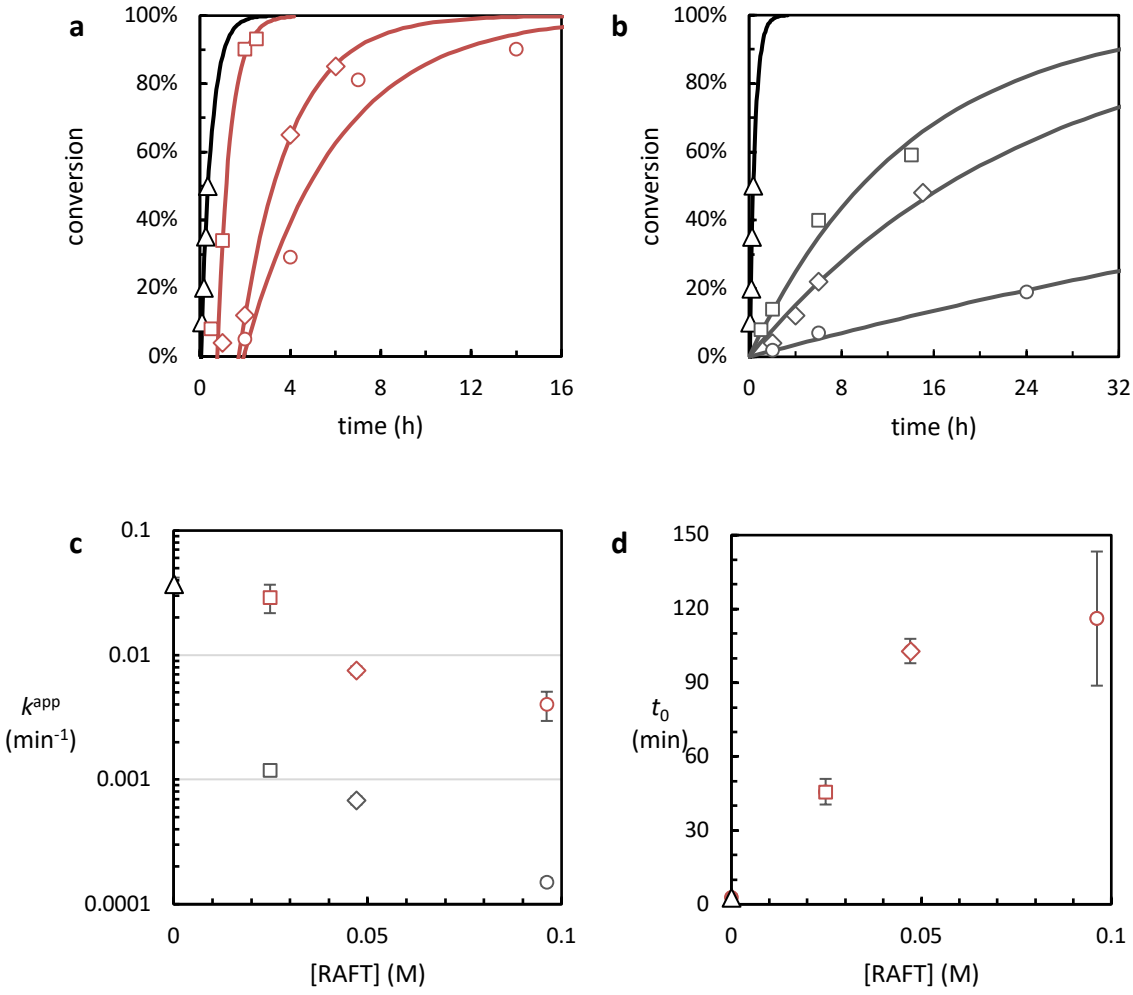


Figure 4. Conversion vs time data for bulk polymerizations of vinyl acetate mediated by **1S** (a) or **1Se** (b) in the presence of 11 mM AIBN at 70 °C. Lines represent best fits to conversion = 0 ($t < t_0$), $1 - \exp[-k^{app}.(t-t_0)]$ ($t \geq t_0$) for polymerizations of **1S** and conversion = $1 - \exp(-k^{app}.t)$ for polymerizations of **1Se**. Fitted values of k^{app} and t_0 are shown in (c) and (d), respectively, for **1S**

(red) and **1Se** (grey, k^{app} only). Different symbols correspond to different initial VAc:**1** ratios (**1S:** square: 442:1; diamond: 233:1; circle: 114:1; **1Se:** square: 464:1; diamond: 231:1; circle: 114:1).

Chain transfer constants of RAFT agents. The relative rates of consumption of RAFT agent, RAFT, and monomer, M, in the early stages of the reaction are given by equation 4:

$$\frac{d[\mathrm{RAFT}]}{d[\mathrm{M}]} = C_{\mathrm{S}} \frac{[\mathrm{RAFT}]}{[\mathrm{M}]+C_S[RAFT]+C_{-S}[R]} \quad (4)$$

In the case where C_{-S} is negligible, this can be simplified to equation 5:

$$\frac{d[\mathrm{RAFT}]}{d[\mathrm{M}]} \approx C_{\mathrm{S}} \frac{[\mathrm{RAFT}]}{[\mathrm{M}]+C_S[RAFT]} \quad (5)$$

This was assumed to be the case for vinyl acetate polymerizations in the presence of **1S** and **1Se**, due to the greater resonance stabilization of the cyanomethyl radical compared to the poly(vinyl acetate) propagating radical. Finally, if [M] >> C_S[R], further simplification is possible to give equation 6:

$$\frac{d[\mathrm{RAFT}]}{d[\mathrm{M}]} \approx C_{\mathrm{S}} \frac{[\mathrm{RAFT}]}{[\mathrm{M}]} \quad (6)$$

This analysis presumes that chain transfer and propagation are the only reactions that consume the monomer and RAFT agent, respectively. The chain transfer constants, C_S, of the RAFT agents were evaluated by measuring RAFT agent conversion, p_R, as a function of monomer conversion, p_M, according to Walling's method.[39,40] This method makes use of the integrated form of equation 6, shown in equation 7. Note that a non-linear relationship has been used rather than the more typical linearized relationship relating ln[R] and ln[M] in order to reduce bias induced by the distortion of the error structure of the data inherent in linearization.[41]

$$(1 - p_R) = (1 - p_M)^{C_S} \quad (7)$$

Monomer conversion was determined by ^{1}H NMR, while RAFT agent conversion was determined from the UV absorbance of the peak corresponding to the RAFT agent in the SEC chromatogram. The values of C_S were calculated by nonlinear least squares fitting, assuming errors of equal magnitude in both variables (Figure 5). The calculated values of C_S are 45 (95% confidence interval = [26, 220]) for **1Se** and 5.4 (95% confidence interval = [4.6, 6.7]) for **1S**. The use of the simplified equation 6 as opposed to equation 5 had a negligible effect on the result (see Supporting Information for details).

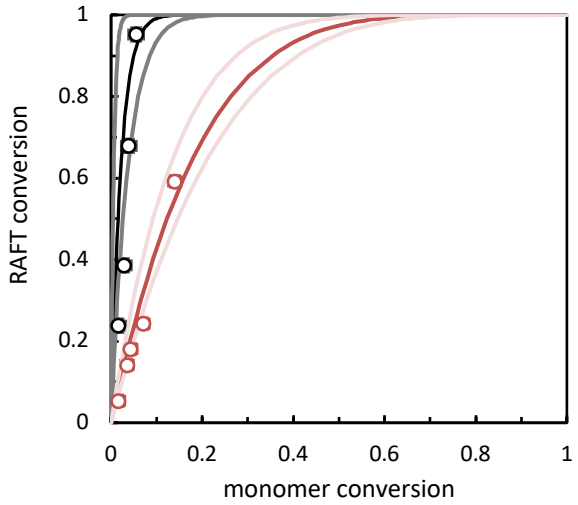


Figure 5. RAFT conversion as a function of monomer conversion for polymerizations of vinyl acetate in the presence of **1Se** (grey) and **1S** (red). Heavy lines represent fits to $(1\text{-}p_R) = (1\text{-}p_M)^{C_S}$, with C_S = 45 and 5.4 respectively. Lighter lines represent 95% confidence limits. Error bars represent the standard error in the data points and correspond to a standard error of 1.5% in the conversion of monomer and RAFT agent.

The measured value of C_S for **1Se** is an order of magnitude greater than that of **1S**, a surprising result given the similar molecular weight distributions obtained for polymers produced with either RAFT agent (Figure 1). The induction times observed in the presence of **1S**, but not in the presence of **1Se**, may provide an explanation for this behavior. Klumperman and coworkers have shown that in the polymerization of VAc in the presence of various xanthate RAFT agents, there is an initial induction period during which the RAFT agent is converted to a species containing exactly one monomer unit.[14] Polymerization of VAc does not begin until all xanthate has been converted to the monoadduct. For this to occur, the rate of addition of the propagating radical to the RAFT agent must be much greater than the rate of propagation (C_S[RAFT]/[M] >> 1), while the rate of addition of the leaving group (in this case cyanomethyl) to the monomer should be slower than the rate of propagation.[15]

It is likely that this process takes place in the **1S** polymerization, in which an induction period is also observed. In this case, the measured chain transfer constant is not that of **1S**, but that of the monoadduct. It would not be possible to distinguish these two species by size exclusion chromatography, as they would elute at similar volumes. In the case of **1Se**, for which no induction period is observed, the measured chain transfer constant is that of **1Se**. In this case, the addition of cyanomethyl to VAc is no longer rate-determining, and no induction period is observed. As the rate of cyanomethyl addition should be independent of the nature of the RAFT agent, this in turn suggests that a different reaction is significantly slower in the case of **1Se**-mediated polymerization and becomes rate-determining. A plausible hypothesis is that the fragmentation of the **1Se** radical adduct is significantly slower than that of the **1S** radical adduct. This would result in increased concentrations of **1Se** radical adducts, leading to higher levels of intermediate radical termination and a slower overall polymerization.

Chain transfer constant of macroRAFT agent. A similar procedure was used to determine the chain transfer constant of macroRAFT agents **2S** and **2Se** obtained from polymerization of VAc in the presence of **1S** and **1Se** (Figure 6). Both macroRAFT agents had a number-average molecular weight of 3750 $g.mol^{-1}$ (determined by SEC), with dispersities of 1.48 (**2S**) or 1.34 (**2Se**). The purified macroRAFT agents were dissolved in a large excess of VAc ([VAc]/[**2**] = 1600) and polymerization was initiated by AIBN at 70°C. Conversion of macroRAFT agent and monomer were determined by analysis of the SEC traces after injection of a known quantity of reaction mixture, following the method developed by Goto and Fukuda.[42-44] Four experiments were carried out for each macroRAFT agent, using different quantities of initiator in each case.

The major limitations of this method are due to the presence of dead chains in the macroRAFT agent, and the difficulty of deconvoluting the SEC traces of the unreacted macroRAFT agent and polymer.[45,46] We estimated the level of dead polymer chains to be 6.8% in the case of **2S**, and 9.3% in the case of **2Se**, based on the known rate constant of decomposition of AIBN of 3.2×10^{-5} s^{-1} at 70°C, and an assumed value of 0.6 for the initiator efficiency (literature values range from 0.25-0.65 at 60°C).[47] The estimated concentration of dead polymer was subtracted from the measured concentration of macroRAFT agent when calculating macroRAFT agent conversion, as recommended by Fukuda.[45] Deconvolution of the chains was facilitated by the use of a large excess of VAc, enabling good separation between the peaks corresponding to the unreacted macroRAFT agent and the chain-extended polymer. All SEC traces are shown in the Supporting Information. While some residual error is inevitable, it should be relatively consistent between the two macroRAFT agents given their similar molecular weight distributions and estimated purities.

A plot of macroRAFT conversion vs monomer conversion (Figure 6) shows that all experiments followed similar trajectories. Values of C_S were obtained by nonlinear least squares fitting of

equation 8, assuming errors of similar magnitude in both variables. The two macroRAFT agents showed similar chain transfer constants, of 3.2 for **2S** and 3.9 for **2Se**, with 95% confidence intervals of [3.0, 3.5] and [3.4, 4.3] respectively. This contrasts with the large apparent difference in C_S observed between **1S** and **1Se**, and supports the idea that the C_S measured for **1S** (5.4) is actually that of the monoadduct produced during the induction period.

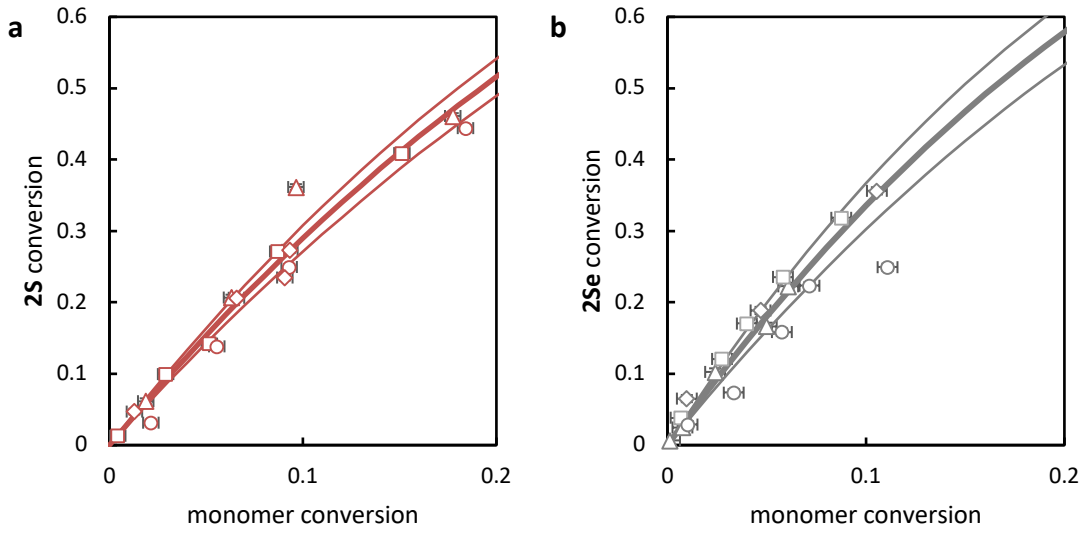


Figure 6. MacroRAFT agent conversion as a function of monomer conversion for polymerizations of VAc in the presence of **2S** (a) and **2Se** (b). Different symbols correspond to experiments carried out at different initiator concentrations. Heavy solid line represents best fit to the equation $(1 - p_2) = (1 - p_M)^{C_S}$, with C_S = 3.2 (**2S**) or 3.9 (**2Se**). Lighter lines represent the 95% confidence intervals for C_S of [3.0, 3.5] (**2S**) and [3.4, 4.3] (**2Se**). Error bars represent the standard error in the data points, and correspond to a standard error of 0.4% (**2S**) or 0.5% (**2Se**) in the measurement of conversion of monomer and RAFT agent.

The weaker C-Se bond found in selenium-based RAFT agents raises the possibility that spontaneous dissociation of the RAFT agent may occur, forming a propagating polyVAc radical

and a relatively persistent selenocarbonylselenyl radical. If this were the case, the measured chain transfer constant, C_S^{app}, would contain a component due to spontaneous dissociation of the RAFT agent.

Following Fukuda's treatment,[42] if the measured rate of RAFT agent consumption, k_a^{app} is assumed to be first order with respect to [RAFT] and [R•], it will contain a component due to chain transfer (k_a[R•]), and a component due to spontaneous dissociation of the RAFT agent (k_d), which is independent of the radical concentration (equation 8).

$$k_a^{app}[R^\bullet] = k_a[R^\bullet] + k_d \quad (8)$$

Dividing both sides of the equation by k_p[R•] gives equation 9:

$$\frac{k_a^{app}}{k_p} = \frac{k_a}{k_p} + \frac{k_d}{k_p[R^\bullet]} \quad (9)$$

which can be expressed in terms of chain transfer constants (measured, C_S^{app}, and underlying, C_S) and the apparent rate constant of polymerization, $k^{app} = k_p[R^\bullet] = -d(\ln[M])/dt$ (equation 10).

$$C_S^{app} = C_S + \frac{k_d}{k^{app}} \quad (10)$$

C_S was evaluated independently for each initiator concentration, then plotted against $1/k^{app}$, with results shown in Figure 7. No dependence of C_S on initiator concentration was observed for either **2S** or **2Se**, indicating that spontaneous dissociation of sulfur- or selenium-based RAFT agents is negligible.

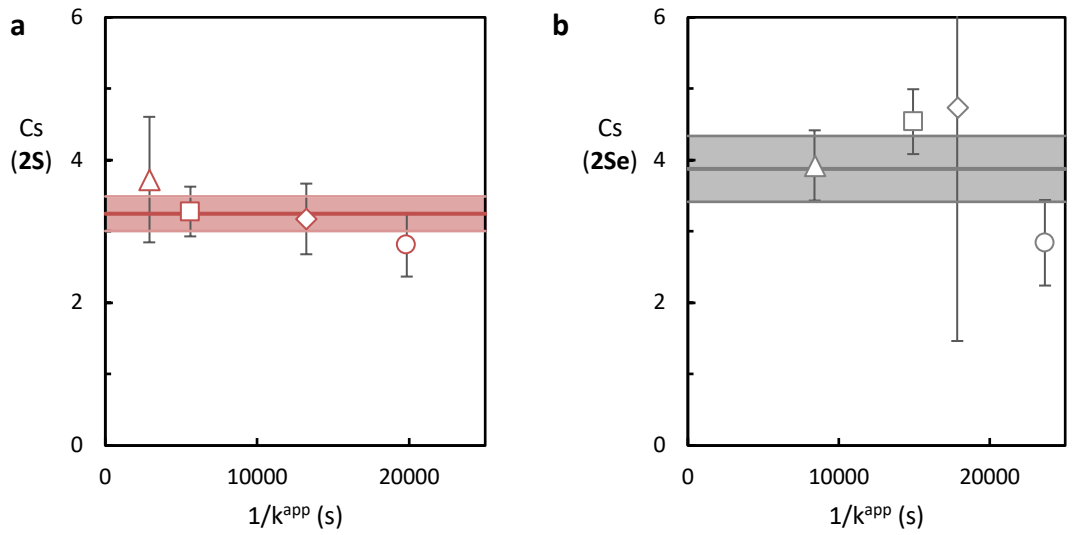


Figure 7. C_S of **2S** (a) and **2Se** (b) plotted for each experiment, as a function of $1/k^{app}$ (inverse of the apparent rate constant of polymerization). Error bars represent 95% confidence intervals for the individual values of C_S. The solid lines represent the C_S obtained by fitting all experimental results, and shaded areas represent the 95% confidence intervals for these values.

For both **2S** and **2Se**, the polymerization kinetics were 0.5-order in initiator concentration, and displayed an induction time, t_0, ranging from a few minutes up to half an hour, which was inversely proportional to the square root of the concentration of AIBN. For a comparable initiator concentration, the **2S** polymerization was approximately three times faster than the **2Se** polymerization (Figure 8). Both **2S** and **2Se** polymerizations were retarded by comparison with the control polymerization at a comparable initiator concentration. Induction periods were approximately twice as long for **2Se** polymerizations as for **2S** polymerizations at a comparable initiator concentration (Figure 8). While the induction periods observed for **1S** could be explained by selective formation of the single monomer adduct, the cause of induction periods in the presence

of macroRAFT agents **2** is unclear. The -0.5-order dependence on AIBN concentration suggests that the length of the induction time is inversely proportional to the radical concentration.

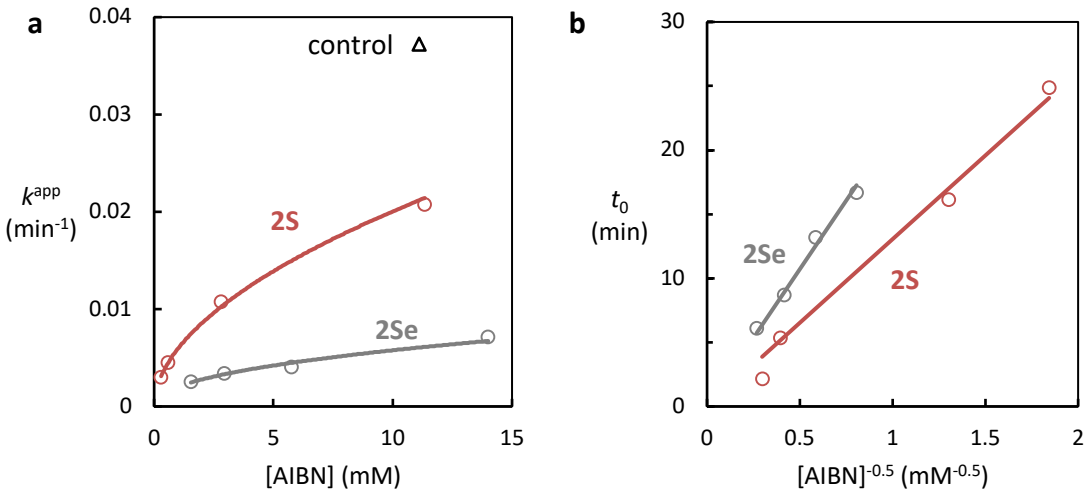


Figure 8. Dependence of (a) apparent first order rate constants, k^{app} and (b) induction times, t_0 on AIBN concentration for polymerizations of VAc in the presence of **2S** (red) and **2Se** (gray) ([2] = 6.4 mM). Dashed lines in figure 6a represent $k^{app} = 5.9 \times 10^{-3}$ [AIBN]$^{0.53}$ min^{-1} (**2S**) and $k^{app} = 2.0 \times 10^{-3}$ [AIBN]$^{0.46}$ min^{-1} (**2Se**). Dashed lines in figure 6b represent $t_0 = 13 \times$ [AIBN]$^{-0.5}$ min (**2S**) and $21 \times$ [AIBN]$^{-0.5}$ min (**2Se**).

These results, together with those obtained for the small molecule RAFT agents **1S** and **1Se**, suggest that significant termination of intermediate radicals occurs, which reduces the concentration of propagating radicals, retarding the polymerization.[18,20,23] This effect is more significant for selenium-based RAFT agents than for their sulfur analogs.

Conclusions

Theoretical studies suggest that dithiocarbamates and diselenocarbamates with the same R and Z groups should exhibit similar reactivities as reversible addition fragmentation chain transfer agents. However, the radical adducts formed from diselenocarbamates are more likely to undergo intermediate radical termination than those formed from dithiocarbamates. In line with these predictions, both the sulfur-based RAFT agent, *S*-cyanomethyl *N*,*N*-dimethyldithiocarbamate (**1S**) and its selenium analogue, *Se*-cyanomethyl *N*,*N*-dimethyldiselenocarbamate (**1Se**) were capable of controlling the polymerization of VAc, providing relatively narrowly dispersed polymers with controlled molecular weight. Polymerizations in the presence of **1Se** were substantially retarded, indicating significant termination of intermediate radicals. By contrast, polymerizations in the presence of **1S** were less retarded, but exhibited induction periods of up to 2 hours. Such induction periods are typically associated with selective formation of a single monomer adduct.

The chain transfer constants of **1S**, **1Se** and the corresponding macroRAFT agents **2S** and **2Se** were measured as 5.4 (**1S**), 45 (**1Se**), 3.2 (**2S**) and 3.9 (**2Se**). The low value measured for **1S** probably represents the C_S of the single monomer adduct, **1S′**, with the true C_S of **1S** being too high to measure using the SEC curve resolution technique. Chain transfer constants for the macroRAFT agents **2** were independent of the radical concentration, indicating that spontaneous dissociation of the RAFT agent is negligible.

These experimental results support the theoretical prediction that the chain transfer constants of selenium-based RAFT agents are generally similar to those of sulfur-based RAFT agents with identical substituents. However, the intermediate radicals resulting from addition of a propagating radical to a selenium-based RAFT agent are significantly more likely to undergo intermediate radical termination, leading to substantial retardation of the polymerization.

Experimental part

The 2,2′-azobis(isobutyronitrile) initiator (AIBN, ≥ 98%) was purchased from Fluka and recrystallized twice from methanol prior use. Vinyl acetate (VAc, 99+%) was purchased from Acros Organics and purified by passing through a column packed with neutral alumina. *S*-cyanomethyl *N*,*N*-dimethyldithiocarbamate was purchased from Aldrich and used as received. *Se*-cyanomethyl *N*,*N*-dimethyldiselenocarbamate was synthesised according to a literature procedure.[12]

Size-exclusion chromatography (SEC) was used to determine the number-average molar mass (Mn) values and dispersities (Đ) of the macroRAFT agents. The SEC analyses were conducted using a Waters 2410 index refractometer and a Waters 2489 UV/Vis spectrometer (at 290 nm) with a Styragel column (HR4E) in tetrahydrofuran (THF) as eluent at a flow rate of 1.0 mL.min^{-1} (35 °C). The column systems were calibrated with narrow polystyrene (PSt) standards, obtained from Polymer Laboratories, ranging from 580 to 164500 g.mol^{-1}. Values of M_n and Đ are reported in PSt equivalents.

Monomer conversion comparison. The polymerizations were performed in glass tubes that were flame-sealed under vacuum after three freeze–pump–thaw cycles. The tubes were immersed into an oil bath at the desired temperature and frozen at given intervals into liquid nitrogen. The monomer conversion was determined by 1H NMR.

A typical procedure for the polymerisations is as follows: **1S** (0.05 g, 0.31 mmol), AIBN (0.01 g, 0.07 mmol) and VAc (6.20 g, 72.08 mmol) were stirred together in a Schlenk tube. The main solution was divided into 5 glass tubes and degased with three freeze-pump-thaw cycles before

being flame-sealed under vacuum. The tubes were placed in an oil bath maintained at 70 °C. At given intervals, the tubes were removed and frozen into liquid nitrogen.

Comparison of VAc and RAFT agent conversion. Polymerizations were performed in glass tubes that were flame-sealed under vacuum after three freeze–pump–thaw cycles. The tubes were immersed into an oil bath at the desired temperature and frozen at given intervals into liquid nitrogen. The monomer conversion was determined by ^{1}H NMR and the RAFT agent conversion was determined by SEC UV.

A typical procedure of the determination of monomer conversion versus RAFT agent conversions is as follows: **1S** (0.03 g, 0.16 mmol), AIBN (0.01 g, 0.08 mmol) and VAc (6.23 g, 72.38 mmol) were stirred together in a schlenk tube. The main solution was divided into 5 glass tubes and degased with three freeze-pump-thaw cycles before being flame-sealed under vacuum. The tubes were placed in an oil bath maintained at 70 °C. At given intervals, the tubes were removed and frozen into liquid nitrogen. The samples were diluted by THF to a known concentration and analysed by SEC.

1Se (0.04 g, 0.16 mmol), AIBN (0.01 g, 0.08 mmol) and VAc (6.23 g, 72.38 mmol) were stirred together in a schlenk tube. The main solution was divided into 5 glass tubes and degased with three freeze-pump-thaw cycles before being flame-sealed under vacuum. The tubes were placed in an oil bath maintained at 70 °C. At given intervals, the tubes were removed and frozen into liquid nitrogen. The samples were diluted by THF to a known concentration and analysed by SEC.

Chain extension and $C_{tr,ex}$ determination

Preparation of **2S**. A glass tube was loaded with **1S** (0.10 g, 0.63 mmol), VAc (2.40 g, 27.91 mmol) and AIBN (0.03 g, 0.15 mmol). After three freeze–pump–thaw cycles, the tube was flame-sealed under vacuum. The tube was immersed into an oil bath at 70 °C for 6 hours before being frozen into liquid nitrogen (conv. 90%). The volatiles were removed under reduced pressure to give a yellow powder. $M_{n,NMR}$ = 3600 g.mol-1, $M_{n,SEC}$ = 3750 g.mol^{-1}, Đ = 1.48. No unreacted **1S** could be observed by NMR or SEC.

Preparation of **2Se**. A glass tube was loaded with **1Se** (0.10 g, 0.38 mmol), VAc (3.70 g, 43.02 mmol) and AIBN (0.04 g, 0.24 mmol). After three freeze–pump–thaw cycles, the tube was flame-sealed under vacuum. The tube was immersed into an oil bath at 70 °C for 2 hours and 45 minutes before being frozen into liquid nitrogen (conv. 35 %). The volatiles were removed under reduced pressure to give an orange powder. $M_{n,NMR}$ = 3600 g.mol^{-1}, $M_{n,SEC}$ = 3750 g.mol^{-1}, Đ = 1.34. No unreacted **1Se** could be observed by NMR or SEC.

A typical procedure of the chain extension polymerization is as follows: **2S** (0.10 g, 0.03 mmol), AIBN (0.01 g, 0.05 mmol) and VAc (4.07 g, 47.28 mmol) were stirred together in a schlenk tube. The main solution was divided into 5 glass tubes and degassed with three freeze-pump-thaw cycles before being flame-sealed under vacuum. The tubes were placed in an oil bath maintained at 70 °C. At given intervals, the tubes were removed and frozen into liquid nitrogen. The samples were diluted by THF to a known concentration and analyzed by SEC.

The total area under each chromatogram relative to the t_0 allows the direct determination of the monomer conversion. We applied the SEC curve resolution method[42] to determine the interchain transfer constant.

Theoretical Procedures. All geometries were optimized using B3-LYP/6-31G(d), except for the kinetics calculations for which M06-2X/6-31G(d) was used instead. For species containing Se, we adopted Rassolov's 6-31G rather than the default version in Gaussian. Rassolov's 6-31G basis set is consistent with the first- and second-row atoms, whereas the default Gaussian 6-31G basis set is not. All conformers were systematically searched and results were only reported for the lowest energy conformers. For Z5, the chair is always lower in energy than the boat form. The enthalpy at 0K was calculated using a modified version of G3(MP2)-RAD, where the ROMP2/G3MP2large calculations were replaced by RI-ROMP2/G3MP2Large with the RIMP2-cc-pVTZ auxiliary basis set. For cases where the full system was too large to be studied with G3(MP2)-RAD (Z3, Z4, Z5, Z11 and Z12), an ONIOM approximation to G3(MP2)-RAD was used in which the full system was treated with ROMP2/G3MP2Large, and the core system (Z1 for Z3-5 and Z9 for Z10 and Z11) was treated with G3(MP2)-RAD.

ASSOCIATED CONTENT

Supporting Information. The following files are available free of charge. Detailed experimental procedures and data for all polymerizations including SEC traces; detailed theoretical calculations including total energies and optimized geometries (pdf).

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Graphical Abstract for Experimental and theoretical comparison of addition-fragmentation pathways of diseleno- and dithiocarbamate RAFT agents

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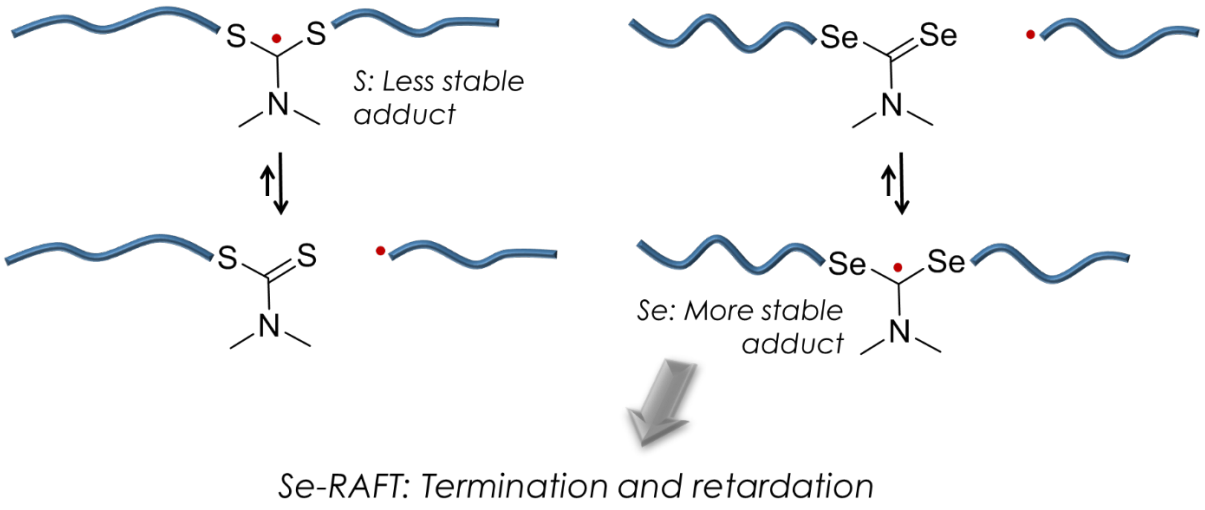

Theoretical studies suggest that identically substituted dithio- and diselenocarbamate RAFT agents will have similar reactivity, but that diselenocarbamate RAFT agents are more likely to undergo intermediate radical termination. These results are supported by an experimental study of polymerizations of vinyl acetate mediated by *Se*-cyanomethyl *N*,*N*-dimethyl diselenocarbamate (**1Se**) and its sulfur analog, *S*-cyanomethyl *N*,*N*-dimethyl dithiocarbamate (**1S**). While the two polymerizations had similar interchain transfer constants (3.2 for **1S** and 3.9 for **1Se**), significant retardation was observed for **1Se**-mediated polymerizations. External chain transfer constants were also measured for **1S** (5.4) and **1Se** (45). The low apparent value of the chain transfer constant of **1S** is attributed to the selective formation of a single monomer adduct in the early stages of the reaction.